Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Psychiatric Disorders

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Background: *Disulfiram and naltrexone are approved by the Food and Drug Administration (FDA) for the treatment of alcoholism, but these agents have not been rigorously evaluated in dually diagnosed individuals.*

Method: *Two-hundred and fifty-four patients with an Axis I psychiatric disorder and comorbid alcohol dependence were treated for 12 weeks in an outpatient medication study conducted at three Veterans Administration outpatient clinics. Randomization included assignment to one of four groups: 1) naltrexone alone; 2) placebo alone; 3) (open-label) disulfiram and (blinded) naltrexone; or 4) (open-label) disulfiram and (blinded) placebo. Medication compliance was evaluated using the Microelectric Events Monitoring System. Primary outcomes were measures of alcohol use. Secondary outcomes included psychiatric symptoms, alcohol craving, g-GGT levels and adverse events.*

Results: *There was a high rate of abstinence across groups. Subjects treated with an active medication had significantly more consecutive weeks of abstinence and less craving than those treated with placebo, but there were no significant group differences in other measures of alcohol consumption. There was no advantage of the combination of both medications.*

Conclusions: *These data suggest a modest advantage for the use of disulfiram and naltrexone for this group of dually diagnosed alcohol-dependent individuals but did not suggest an advantage in the combination.*

Key Words: Alcohol, comorbidity, disulfiram, dual diagnosis, naltrexone

Following preclinical studies suggesting that naltrexone may be an effective pharmacologic agent in treatment of alcohol dependence, the efficacy of naltrexone in reducing alcohol use in alcohol-dependent individuals was demonstrated in two well-known clinical trials (Volpicelli et al 1992; O'Malley et al 2002). Naltrexone was subsequently the second medication approved by the Food and Drug Administration (FDA) for use in treating alcohol dependence. A meta-analysis of all published placebo-controlled trials using naltrexone up to 2000 suggested that naltrexone has a modest positive effect on alcohol consumption (e.g., effect size for percentage drinking days = –.191, $p <$ .001; Kranzler and Van Kirk 2001). Naltrexone has not been uniformly effective, however. For example, a large multisite trial in alcohol-dependent veterans failed to confirm any effect of naltrexone on drinking outcomes (Krystal et al 2001).

The safety and effectiveness of naltrexone in alcohol-dependent populations with major mental illness is an important clinical question. These individuals constitute a large number of those seeking treatment in substance abuse programs (McKellar 2003), and these patients have mostly been excluded from clinical trials evaluating pharmacotherapies for alcohol dependence. Some evidence is emerging, however. A few pilot studies including open-label reports, chart review studies, and a large safety study suggest that naltrexone is safe in patients with alcoholism and comorbid severe mental illness (Croop et al 1997; Salloum et al 1998; Maxwell and Shinderman 2000; Morris et al 2001). A small controlled clinical trial has shown naltrexone to be effective in reducing alcohol consumption and craving compared with placebo in patients with alcohol dependence and comorbid schizophrenia (Petrakis et al 2004). A large administrative review of naltrexone utilization in the Department of Veterans Affairs nationally demonstrated a low overall rate of naltrexone use (<2%), but clinicians were more likely to use it in patients with comorbid Axis I psychiatric diagnoses and in those who have had recent psychiatric inpatient hospitalization (Petrakis et al 2003). This suggests that in an ordinary clinic setting, naltrexone use is associated with comorbid Axis I psychiatric conditions, demonstrating the need for a rigorous study of its efficacy in this population.

Disulfiram, the other medication approved by the FDA for the treatment of alcohol dependence, has been used clinically in the management of patients with alcohol dependence for 50 years (Meyer 1989). Disulfiram's support from clinical trials has been mixed, with a landmark multisite study reporting that disulfiram was not superior to placebo in reducing alcohol use (Fuller et al 1986). In fact, positive clinical outcomes were found only for those individuals who complied with disulfiram. Studies in which compliance is facilitated through compliance contracts, mandates, or methadone delivery have suggested disulfiram's efficacy (Ling and Weiss 1983; O'Farrell and Bayog 1986; Chick et al 1992; Petrakis et al 2000). Like naltrexone, disulfiram has not been rigorously tested in individuals with psychiatric comorbidity. Early reports suggested disulfiram may precipitate or worsen psychosis in schizophrenia patients (Larson et al 1992), whereas other reports suggest it may be used safely in patients with comorbid psychiatric disorders (Larson et al 1992; Mueser et al 2003). To our knowledge, naltrexone and disulfiram have not been systematically compared or tested together in combination for alcohol dependence. These two medications have a very different mechanism of action, and each may have a unique contribution in the treatment of alcoholism. Self-administration, human laboratory, and retrospective patient reports from clinical trials have provided evidence for a potential mechanism of action for naltrexone. Naltrexone appears to reduce the rewarding effects of alcohol consumption and the ability of initial alcohol consumption to prime for further drinking (Swift et al 1994; Volpicelli et al 1995; Davidson et al 1996; O'Malley et al 1996, 2002). In contrast with disulfiram, naltrexone does not lead to a powerful aversive reaction if patients consume alcohol. Patients

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may thus be more willing to initiate naltrexone treatment and to continue to take the medication because they know that drinking is not prohibited. Disulfiram, on the other hand, may be more effective in promoting abstinence in individuals motivated for treatment but may appeal to fewer patients and lead to more discontinuation of treatment. Medication compliance has influenced the efficacy of both medications (Fuller et al 1986; Chick et al 1992; Volpicelli et al 1997).

We conducted a multicenter controlled trial of the efficacy of naltrexone and disulfiram alone and in combination in individuals with major Axis I disorders and comorbid alcohol dependence in a general clinic (i.e., nonresearch) setting. In this 12-week outpatient study, individuals were randomized to one of four groups: 1) naltrexone alone; 2) placebo alone; 3) disulfiram and naltrexone; or 4) disulfiram and placebo. The use of a placebo control condition for disulfiram may lead to the temptation for individuals to sample alcohol to "test" the blind, leaving questions about the safety and the ability to have a true medication blind using this design. Therefore, individuals were randomized to either disulfiram or no disulfiram, and disulfiram was dispensed in an open-label fashion. The dispensing of naltrexone was placebo-controlled and double-blind. We evaluated the following hypotheses: 1) either medication condition would yield superior drinking outcomes when contrasted with inactive medication, 2) naltrexone would be superior to disulfiram in indices of patient acceptance and craving and would result in fewer heavy drinking days, and 3) combination treatment would be superior to either treatment alone because it would combine the abstinence-initiating effect of disulfiram with the antipriming effects of naltrexone. Furthermore, because disulfiram was dispensed in an open fashion, we could evaluate the relative acceptability and efficacy of each treatment because patients in the combined medication group could discontinue disulfiram while still complying with naltrexone treatment if they planned to drink.

Methods

Subjects

This study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Northampton and Bedford, Massachusetts, VAs, which are all affiliated with the New England Mental Illness and Research Education Clinical Center (MIRECC). Subjects were recruited from the patients who were treated in clinics at these MIRECC facilities. Subjects met current DSM-IV criteria for a major Axis I disorder and current DSM-IV criteria for alcohol dependence. These diagnoses were determined by structured clinical interview (Spitzer et al 1992). Subjects had been abstinent no more than 29 days. Those subjects on psychiatric medications had to be on a stable regimen for at least 2 weeks before randomization. Exclusion criteria were unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone and disulfiram, including liver function tests $>$ 3 times the normal level. Those subjects on psychiatric medications had to be on a stable regimen (no medication changes) for at least 2 weeks before randomization. Subjects were also required to be abstinent for 3 days before randomization, and the stated goal of the study was complete abstinence.

Because subjects were recruited from the clinics at the three VA sites, participants in the trial continued to receive psychiatric treatment as usual. All three clinics have intensive substance abuse treatment programs that include an intensive rehabilitation program with aftercare and supported housing options for patients in treatment. Most subjects were already enrolled in the clinics before signing informed consent, although a few responded to advertisements and entered treatment as a result of entering into the trial.

After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments, and an interview with a psychiatrist. Of the 567 patients meeting initial eligibility criteria, 313 declined to participate or were deemed ineligible, and 254 were randomized. As shown in Figure 1, of those who were not randomized, the most common reasons were an unwillingness to be randomized (n = 98) or take the study medications (n = 78). In addition, 43 individuals had medical conditions that precluded participation, 43 did not have a current comorbid Axis I psychiatric disorder, 18 did not meet criteria for alcohol dependence, 33 individuals could not maintain the 3-day sobriety requirement before randomization, 24 individuals were using opiates, 23 were deemed as cognitively impaired and unable to participate, and 9 were psychiatrically unstable. Other reasons included no reliable transportation (n = 36), moving within the next 6 months (n = 15), facing possible incarceration (n = 15), or not eligible for VA services (n = 9). Individuals may have had more than one reason for exclusion from participation.

Treatments

Following completion of these baseline assessments, 254 subjects were randomized to one of four groups for a 12-week trial. Randomization included 1) open randomization to disulfiram 250 mg or no disulfiram, and 2) randomization to naltrexone 50 mg or placebo in a double-blind fashion. This resulted in the following groups: naltrexone alone, placebo alone, disulfiram and naltrexone, or disulfiram and placebo.

The randomization was done simultaneously, and those subjects who were on disulfiram were given two study bottles and started both medications on the first day of randomization. Medications were stored in separate bottles for each study medication and clearly labeled as "disulfiram" or "naltrexone study medication." Medication compliance was assessed using Microelective Events Monitoring (MEMS) caps at each visit. All subjects were informed of how their medication compliance would be monitored and also received weekly Clinical Management/Compliance Enhancement therapy (Carroll et al 1998) administered by research personnel.

Assessments

Primary outcomes were measures of alcohol use. The Substance Abuse Calendar, based on the Timeline Follow-Back Interview (Sobell and Sobell 1992), was administered by a research assistant at each weekly visit to collect a detailed self-report of alcohol and other substance use throughout the 84-day treatment period as well as for the 90-day period before randomization. Although data on alcohol consumption was available for the 90-day period before randomization occurred, most patients decreased their alcohol use because they had already entered treatment. Therefore, the first 30 days of this baseline period is more representative of their actual baseline alcohol consumption. Craving was assessed weekly using the Obsessive Compulsive Drinking Scale (OCDS; Anton et al 1996).

Psychiatric symptoms were assessed using the Brief Symptoms Inventory (BSI; Derogatis and Melisaratos 1983) administered by the research staff at the baseline and biweekly during

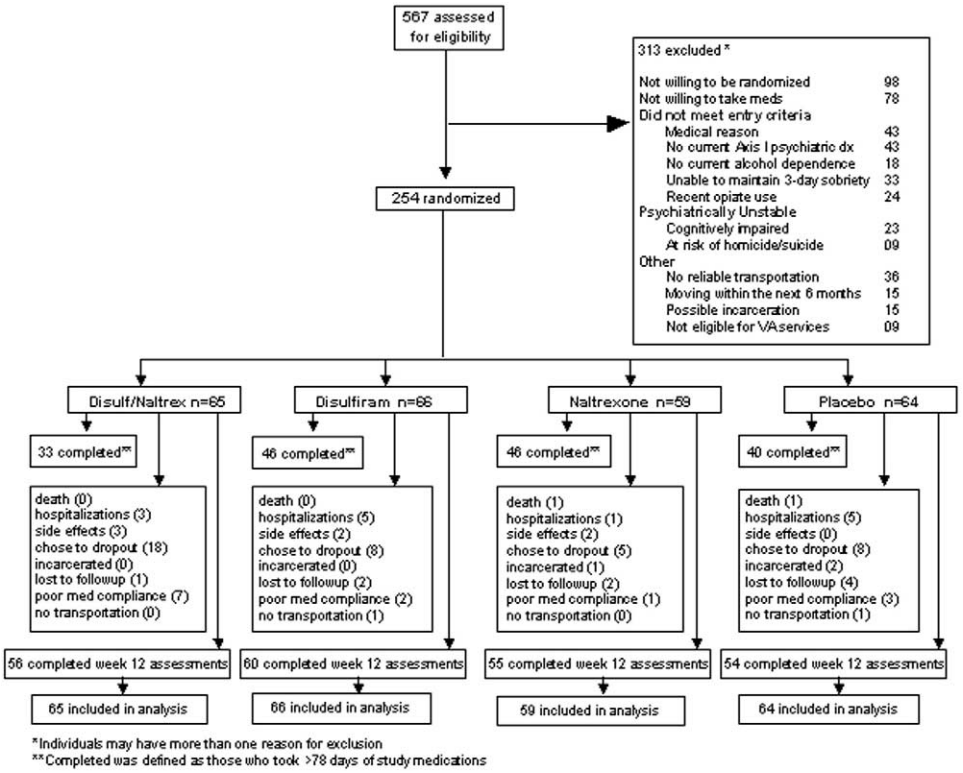

Figure 1. Trial flow diagram of alcohol dependent subjects with comorbid Axis I disorders by treatment group. Trial completers were defined as those who took at least 78 days (11 weeks and 1 day) of medication.

treatment. Side effects and common adverse symptoms were evaluated by the research staff weekly using Hopkins Symptom Checklist (Derogatis et al 1974), a self-report symptom inventory. The symptoms that are known to be associated with naltrexone and disulfiram treatment were specifically screened for and included abdominal pain, nausea, vomiting, loss of appetite, constipation, diarrhea, nervousness, restlessness, difficulty sleeping, feeling drowsy, fatigue, anger, depression, confusion, tearing, sneezing, runny nose, muscle ache, sweating, rash, itching, aftertaste, dry mouth, sexual problems, headache, tremors, blurred vision, numb limbs, pins or needles, night sweats, fever, chills, cough blood, vomit blood, tarry stool, light stool, yellow eyes, irregular heart beat, and dizziness.

Data Analysis

Baseline demographic and substance use variables were compared among treatment groups using chi-square analyses for dichotomous and analysis of variance for continuous variables. The primary outcome variables were maximum consecutive days of abstinence, percent days abstinent, percent heavy drinking days (defined as five or more standard drinks), and number of subjects with total abstinence, calculated from the substance abuse calendar data. Continuous primary and secondary outcomes (e.g., BSI scores, serum levels, OCDS scores) were analyzed using random effects regression models (Hedeker et al 1991) of a priori contrasts for the intent to treat sample. The primary contrasts were 1) the combination of disulfiram/naltrexone versus either disulfiram or naltrexone alone, 2) disulfiram alone versus naltrexone alone, and 3) any medicine versus placebo. Analyses of variance (ANOVA) models were used for single time point continuous outcomes (e.g., days in treatment, consecutive days of abstinence, adverse events). For those collected over time (serum levels, OCDS scores, BSI scores), random effects regression models (baseline through week 12) were used, and thus treatment effect was indicated by a group by time interaction.

Results

Participants

The subjects for this study were 254 veterans recruited at the three New England MIRECC sites: West Haven, Connecticut (n = 80; 31.4%), Northampton, Massachusetts (n = 79; 31.1%), and Bedford, Massachusetts (n = 96; 37.8%). As shown in Table 1, 247 (97.2%) of the subjects were men, 189 (74.1%) were Caucasian, 43 (16.9%)of the subjects were African American, 12 (4.7%) were Hispanic, and 10 (3.9%) were another ethnicity. They had an average age of 47.0 (SD = 8.2). The majority (178; 70.1%) met DSM-IV criteria for major depression, 109 (42.9%) met DSM-IV criteria for posttraumatic stress disorder (PTSD), 49 (19.3%) met DSM-IV criteria for bipolar disorder, 18 (7.4%) met DSM-IV criteria for schizophrenia or schizoaffective disorder, and 50 (19.7%) met DSM-IV criteria for cocaine dependence. Seventy-six subjects (29.9%) had more than one psychiatric diagnosis. There were no significant differences between treatment groups on these demographic and psychiatric variables, with the single exception of the diagnosis of schizophrenia or schizoaffective disorder. Although significantly more participants with these diagnoses were assigned to the naltrexone group (p = .04), it should be noted that the number of individuals with these disorders was small (n = 18).

Two hundred and twenty (87.6%) subjects were prescribed psychiatric medications during the study. Of these, 189 (75.3%) were on antidepressants, 87 (34.7%) were taking mood stabiliz-

Table 1. Baseline Characteristics

	Total Sample ($n = 254$)		Disulfiram/Naltrexone ($n = 65$)		Disulfiram ($n = 66$)		Naltrexone ($n = 59$)		Placebo ($n = 64$)		Statistics	
Variable	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*F*	*p*
Age		47.0 (8.2)		48.2 (9.3)		45.8 (9.0)		47.7 (7.4)		46.2 (7.3)	1.23	.30
Gender											χ^2	*p*
Male	247 (97.2)		63 (96.9)		64 (97.0)		56 (94.9)		64 (100)		3.05	.38
Female	7 (2.8)		2 (3.1)		2 (3.0)		3 (5.1)		0 (0)			
Ethnicity											χ^{2a}	*p*
Caucasian	189 (74.4)		45 (69.2)		51 (77.3)		41 (69.5)		52 (81.3)		3.52	.32
African American	43 (16.9)		15 (23.1)		11 (16.7)		10 (16.9)		7 (10.9)			
Hispanic	12 (4.7)		3 (4.6)		2 (3.0)		2 (3.4)		5 (7.8)			
Other	10 (3.9)		2 (3.1)		2 (3.0)		6 (10.2)		0 (0)			
Psychiatric Diagnosis											χ^2	*p*
Major depression	178 (70.1)		43 (66.2)		51 (77.3)		39 (66.1)		45 (70.3)		2.55	.46
PTSD	109 (42.9)		28 (43.1)		28 (42.4)		29 (49.2)		24 (37.5)		1.71	.63
Cocaine	50 (19.7)		15 (23.1)		14 (21.2)		11 (18.6)		10 (15.6)		1.28	.73
Schizophrenia/schizoaffective	18 (7.1)		3 (4.6)		2 (3.0)		9 (15.3)		4 (6.3)		8.30	.04
GAD/panic disorder	57 (22.4)		13 (20.0)		17 (25.8)		13 (22.0)		14 (21.9)		.66	.88
Bipolar disorder	49 (19.3)		15 (23.1)		17 (25.8)		7 (11.9)		10 (15.6)		5.01	.17
Measures of alcohol consumption											*F*	*p*
Years of use (lifetime)		25.9 (9.5)		26.4 (9.6)		26.2 (9.2)		26.8 (8.6)		25.7 (10.9)	.11	.95
Drinking days (out of 30)		15.8 (12.0)		15.2 (11.7)		15.6 (11.9)		17.4 (12.3)		15.2 (12.1)	.42	.74
Drinks per drinking day		19.4 (12.5)		18.0 (11.3)		18.4 (12.8)		21.1 (14.3)		20.3 (11.6)	.64	.59
% heavy drinking days		89.8 (25.2)		90.4 (24.0)		87.0 (29.3)		91.9 (24.5)		90.4 (22.8)	.32	.81
GGT ($n = 190$)												
Pre				73.9 (58.0)		93.5 (136.5)		53.8 (51.6)		56.0 (69.8)		
Post				35.1 (24.3)		48.3 (65.2)		36.1 (29.3)		45.7 (95.9)		
ADS Score		21.7 (8.9)		19.9 (9.3)		21.9 (8.7)		23.7 (8.2)		21.3 (9.2)	1.86	.14
Prescribed Psychiatric Meds (baseline)												
Any	220 (87.6)		54 (84.4)		61 (93.8)		49 (83.1)		56 (88.9)		4.18	.24
Antidepressants	189 (75.3)		43 (67.2)		54 (83.1)		42 (71.2)		50 (79.4)		5.47	.14
Antianxiety	27 (10.8)		3 (4.7)		10 (15.4)		4 (6.8)		10 (15.9)		6.60	.09
Mood stabilizers	87 (34.7)		21 (32.8)		26 (40.0)		17 (28.8)		23 (36.5)		.90	.59
Antipsychotics	58 (23.1)		11 (17.2)		16 (24.6)		15 (25.4)		16 (25.4)		1.71	.63
Prescribed $>$ 1 type of psych. med	113 (44.5)		20 (31.3)		36 (55.4)		23 (39.0)		31 (49.2)		8.94	.03

GAD, generalized anxiety disorder; GGT, gamma-glutamyl transferase; PTSD, posttraumantic stress disorder; ADS, Alcohol Dependence Scale.
[a]White versus other.

ers, 58 (23.1%) were on antipsychotics, and 27 (10.8%) were on antianxiety medication including benzodiazepines. One hundred and thirteen (44.5%) subjects were prescribed more than one class of medications, and 119 (47.4 %) experienced a change in psychiatric medication during the study. The only significant difference in medication pattern across the four groups was a baseline difference in the percent of subjects who were on more than one type of psychiatric medication. Those in the combination (naltrexone and disulfiram) group had the fewest subjects on more than one type of medication (20; 31.3%), and those in the disulfiram group had the highest percentage (36; 55.4%) on more than one medication ($p = .03$).

As a measure of baseline substance use, drinking data were reported for the first 30 days of the baseline data collected for 90 days before they entered treatment. Subjects as a group drank on average 15.8 (SD = 12.0) days in 30 days and had 89.8% (SD = 25.2) heavy drinking days and consumed a mean of 19.4 (SD = 12.5) standard drinks per drinking day (see Table 1). Subjects as a whole reported a mean of 25.9 (SD = 9.5) years of regular alcohol use, and a mean 21.7 (SD = 8.9) on the Alcohol Dependence Scale. At baseline, subjects as a group ($n = 190$, because of missing values) had a mean level of 69.2 (SD = 87.0) serum gamma-glutamyl transferase (GGT). There were no significant differences in these baseline alcohol use variables among the medication groups.

Treatment Exposure

Of the 254 subjects who were randomized, 165 (65.0%) subjects completed treatment, and 225 (88.6%) were assessed for outcomes at the completion of the study. "Completers" were defined as those who took at least 78 days (11 weeks and 1 day) of medication based on the MEMS data. As shown in Figure 1, of the 89 subjects who did not complete the trial, 13 were considered "noncompleters" because they were compliant with medication for less than 78 days; there were 11 serious adverse events (three subjects with serious adverse events completed the study), 3 subjects chose to drop out to have elective surgery, 39 chose to drop out for reasons other than side effects from the medications, 8 chose to drop out because of side effects, 10 were lost to follow-up, 2 had transportation difficulties, and 3 were incarcerated. Treatment retention was defined as the number of days between the first and last medication dose taken based on the MEMS data. There was a significant difference in treatment retention where subjects assigned to the combination of disulfiram and naltrexone had a shorter duration of treatment than those assigned to disulfiram and placebo and naltrexone alone [$F(1,247) = 7.84$, $p = .01$]. A measure of medication adherence for each study medication (disulfiram and naltrexone study medication) using MEMS data was computed by dividing the number of days pills taken by the number of potential medication days (84 days for all subjects). The overall rate of medication compliance was 82.7% (SD = 26.1). There were no significant differences in medication compliance between the subjects on active medication or on placebo, between the subjects on the combination of medications compared with those on only one active medication, or between the subjects taking naltrexone versus disulfiram (see Table 2).

Alcohol Use and Craving Outcomes

As a group, subjects significantly decreased their alcohol use from baseline to posttreatment in all outcome measures in all self-report measures. There was a high overall rate of abstinence (177 or 69.7% of total sample reported 100% abstinence) during the active phase of the study. As shown in Table 2, subjects assigned to either of the active medications had significantly better drinking outcomes than those subjects in the placebo group. Specifically, participants assigned to either naltrexone or disulfiram reported significantly fewer drinking days per week [$F(1,246) = 5.71$, $p = .02$] and more consecutive days of abstinence [$F(1,246) = 4.49$, $p = .04$] than those assigned to placebo. There were no significant differences in the percent days of abstinence, percent of heavy drinking days, and the number of subjects with total abstinence between groups. There were no advantages in any of the measures of alcohol consumption for subjects who received both medications compared with those treated with either active medication alone. Because of the high rate of abstinence, measures of quantity of alcohol consumption were of questionable significance and are therefore not reported. Analyzing the data excluding those individuals with comorbid cocaine dependence ($n = 204$) did not change the alcohol use outcomes.

Regarding biological measures, participants assigned to disulfiram showed greater reductions over time of GGT [$F(1,454) = 5.85$, $p < .02$] in comparison with those assigned to naltrexone. Moreover, those assigned to the combination tended to have greater reduction of GGT over time compared with those treated with either medication, but this difference was not statistically significant.

Based on the OCDS (Anton et al 1995), disulfiram-treated subjects reported a significantly greater change over time in craving compared with the naltrexone-treated subjects ($z = 3.98$, $p < .01$). There were no significant differences in the total OCDS scores over time between those treated with both medications and those treated with either active medication alone or in those treated with any medication compared with those treated with an inactive medication. Based on the OCDS subscales, disulfiram-treated subjects reported significantly lower scores over time in the Drinking Compulsion subscale ($z = –3.39$, $p < .01$) and the Obsessive subscale ($z = –3.90$, $p < .01$) than the naltrexone-treated subjects, and those subjects treated with any active medication reported significantly lower scores over time on the Drinking Obsessions subscale compared with those treated with no active medication ($z = –2.65$, $p = .01$).

Site analyses revealed treatment differences by site in the outcomes of consecutive days of abstinence and number of subjects with total abstinence; however, there was no site-by-treatment interaction in these alcohol use outcomes.

Measures of Psychiatric Symptoms

As shown in Table 3, subjects as a group reported a significant decrease in measures of psychopathology using the BSI from baseline to posttreatment in each of the subscales, including depression, anxiety, global severity index, interpersonal sensitivity, somatization, obsessive–compulsive, phobic anxiety, and paranoid ideation. Over the course of treatment, subjects treated with either of the active medications had significantly lower scores of paranoid ideation over time than those treated with placebo ($z = 2.37$, $p = .02$). Subjects treated with disulfiram experienced significantly fewer symptoms over time in the obsessive–compulsive ($z = 2.08$, $p = .04$) and phobic anxiety subscales ($z = 2.40$, $p = .02$), whereas those treated with the combination of medications experienced significantly higher levels of depression over time ($z = 2.68$, $p = .01$) and higher scores in the global severity index over time ($z = 1.93$, $p = .05$) subscales than those treated with either medication alone.

Table 2. Primary Outcome Variables

Variable	Disulfiram/Naltrexone ($n = 65$) Mean (SD)	Disulfiram/Placebo ($n = 66$) Mean (SD)	Naltrexone ($n = 59$) Mean (SD)	Placebo ($n = 64$) Mean (SD)	Change over time z, p	Treatment Contrasts: DN vs. DP or N F, p	Treatment Contrasts: DP vs. N F, p	Treatment Contrasts: Any med vs. P F, p
Self-reported drinking								
Consecutive days of abstinence	69.2 (24.0)	70.5 (24.1)	67.2 (25.5)	61.0 (30.3)		.01, .94	.17, .68	4.49, .04
% Days abstinent	96.6 (8.7)	96.6 (10.5)	95.4 (11.8)	93.5 (14.0)		.14, .71	.36, .55	2.78, .10
% Heavy drinking days	3.1 (8.1)	3.2 (10.5)	4.0 (11.4)	5.9 (12.9)		.10, .76	.20, .65	2.48, .12
Subjects with total abstinence, *n*	46 (70.8)	51 (77.3)	38 (64.4)	42 (65.6)		.00, .95	2.55, .11	.67, .41
						Treatment Contrasts Time		
Serum Levels						DN vs. DP	DP vs. N	Any med vs. P
GGT ($n = 217$)						z, p	z, p	z, p
Pre	73.8 (58.0)	93.5 (136.5)	53.8 (51.6)	56.0 (69.8)	14.31, .00	3.55, .06	5.86, .02	0.44, .51
Post	35.1 (24.3)	48.3 (65.2)	36.1 (29.3)	45.7 (95.9)				
SGOT ($n = 253$)								
Pre	35.3 (36.1)	32.8 (23.8)	32.0 (14.7)	34.8 (30.0)	2.05, .10	.03, .85	.26, .61	0.17, .68
Post	27.5 (12.9)	27.4 (15.9)	26.2 (12.8)	37.6 (46.4)				
SGPT ($n = 252$)								
Pre	34.6 (17.8)	39.4 (34.9)	32.8 (17.8)	38.9 (34.0)	7.54, .00	.05, .82	2.42, .12	5.48, .02
Post	29.9 (15.9)	32.1 (32.8)	27.9 (20.8)	39.4 (43.3)				
OCDS factor scores ($n = 254$)								
Total score								
Pre	13.2 (8.4)	13.1 (9.4)	12.4 (7.8)	13.0 (7.7)	−18.84, .00	−1.48, .14	−3.98, .00	−1.44, .15
Post	5.8 (7.8)	4.1 (5.6)	6.1 (7.3)	4.9 (7.7)				
Obsessive score								
Pre	6.1 (4.0)	6.5 (4.5)	6.1 (3.9)	5.9 (3.5)	−17.58, .00	−.85, .39	−3.90, .00	−2.65, .01
Post	2.8 (3.7)	2.3 (2.7)	3.1 (3.7)	2.4 (3.7)				
Compulsive score								
Pre	7.1 (4.9)	6.6 (5.5)	6.2 (4.7)	7.1 (5.0)	−16.26, .00	−1.75, .08	−3.39, .00	−.20, .84
Post	3.0 (4.4)	1.9 (3.2)	3.0 (3.9)	2.5 (4.3)				
Treatment Retention						F, p	F, p	F, p
Days between first and last pill	61.1 (28.0)	70.2 (24.5)	73.7 (22.8)	68.2 (25.7)		7.84, .01	.60, .44	.00, .97
% Days Medication Compliance								
Disulfiram	72.5 (30.4)	80.1 (27.2)	—	—		2.24, .14		
Naltrexone	76.3 (29.8)	—	82.3 (27.4)	—		1.34, .25		
Placebo	—	77.8 (31.4)	—	86.1 (20.0)		3.04, .08		

D, disulfiram; GGT, gamma-glutamyl transferase; N, naltrexone; OCDS, Obsessive Compulsive Drinking and Abstinence Scale; P, placebo; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Table 3. Secondary Outcome Variables

Variable	D/N	D/P	N	P	Change over Time	Statistics: Treatment Contrasts Time: DN vs. D or N	D vs. N	Any med vs. P
						z, p	*z, p*	*z, p*
BSI score								
Depression								
Pre	1.25	1.48	1.54	1.34	−14.68, .00	−2.68, .01	1.68, .09	.81, .42
Post	.61	.89	.93	.65				
Anxiety								
Pre	.85	.99	1.02	.84	−11.97, .00	−.71, .48	.63, .53	−.50, .62
Post	.54	.52	.69	.41				
Global Severity Index								
Pre	.94	1.07	1.04	.98	−15.72, .00	−1.93, .05	1.71, .09	.29, .77
Post	.54	.61	.69	.48				
Interpersonal Sensitivity								
Pre	.92	1.15	1.03	1.02	−11.85, .00	−.47, .64	.44, .66	.28, .78
Post	.56	.64	.68	.51				
Somatization								
Pre	.59	.50	.53	.54	−6.47, .00	−1.70, .09	1.29, .20	−.93, .35
Post	.44	.29	.39	.27				
Obsessive–Compulsive								
Pre	1.1	1.32	1.18	1.14	−14.50, .00	−1.56, .12	2.08, .04	−.50, .62
Post	.69	.74	.82	.49				
Phobic Anxiety								
Pre	.68	.84	.71	.71	−9.61, .00	−1.37, .17	2.40, .02	.90, .37
Post	.42	.41	.53	.42				
Paranoid Ideation								
Pre	.91	.99	.94	.89	−9.53, .00	−1.63, .10	1.23, .22	2.37, .02
Post	.6	.61	.69	.57				
Symptom Questionnaire, percent of patients reporting:						*F, p*	*F, p*	*F, p*
Abdominal Pain	65.6	42.9	49.1	40.3		6.59, .01	.42, .49	2.82, .10
Aftertaste	59.4	47.6	52.6	52.6		1.45, .23	.31, .58	5.91, .02
Blurred Vision	64.1	47.6	59.6	41.9		1.85, .18	1.77, .19	4.37, .04
Confusion	75.0	82.5	82.5	64.5		1.30, .26	.00, .99	6.19, .01
Constipation	51.6	44.4	43.9	29.0		.95, .33	.004, .95	5.93, .02
Drowsy	92.2	90.5	89.5	80.6		.20, .66	.29, .87	4.52, .04
Dry Mouth	79.7	76.2	77.2	62.9		.20, .66	.02, .9	5.29, .02
Fever	34.4	41.3	22.8	32.3		.10, .75	4.63, .03	.004, .95
Irregular Heart	56.3	30.2	36.8	33.9		9.30, .003	.58, .45	1.03, .31
Loss of Appetite	64.1	68.3	75.4	54.8		1.13, .29	.69, .41	4.33, .04
Nausea	76.6	58.7	57.9	41.9		6.03, .02	.009, .92	10.09, .002
Nervousness	79.7	79.4	98.2	79.0		2.63, .11	8.08, .005	1.65, .20
Numb Limbs	64.1	39.7	52.6	45.2		5.45, .02	2.05, .15	.92, .34
Pins or Needles	64.1	38.1	49.1	50.0		7.12, .008	1.48, .22	.003, .96
Restlessness	78.1	84.1	98.2	82.3		5.86, .02	4.91, .03	.84, .36
Tremors	53.1	50.8	57.9	38.7		.03, .88	.61, .44	4.33, .04
Vomiting	42.2	31.7	24.6	24.2		3.88, .05	.73, .39	1.60, .21

BSI, Brief Symptom Inventory; D, disulfiram; N, naltrexone; P, placebo.

Safety and Side Effects

There were 14 serious adverse events in this study. In the disulfiram and naltrexone group, two subjects had cardiac events requiring hospitalization, and one had a disulfiram–alcohol reaction necessitating hospitalization. In the disulfiram and placebo group, four had psychiatric hospitalizations (two for a change in mental status and two for suicidal ideation), one had a cardiac event, and one was hospitalized for acute axonal neuropathy. In the naltrexone alone group, one subject died, and in the placebo only group, there was one death, one drug and alcohol overdose, and one medical hospitalization for pneumonia. Neither of the deaths was determined to be study related (one was taking placebo, the other had been noncompliant with the study, including the medication, for many weeks). Two of the nonfatal cardiac events occurred after patients had discontinued study medications for other reasons, and the other occurred in the context of heavy cocaine use. Three individuals with psychiatric hospitalizations completed the study.

Overall, 96.9% of subjects reported experiencing one or more symptoms potentially related to medication side effects, with depression (88.2%) the most common complaint. As shown in Table 3, subjects taking the combination of disulfiram and

naltrexone were significantly more likely to report abdominal pain [$F(1,242) = 6.59$, $p = .01$], nausea [$F(1,242) = 6.03$, $p = .02$], vomiting [$F(1,242) = 3.88$, $p = .05$], numb limbs [$F(1,242) = 5.45$, $p = .02$], pins and needles [$F(1,242) = 7.12$, $p = .008$], irregular heart beat [$F(1,242) = 9.30$, $p = .003$], and restlessness [$F(1,242) = 5.86$, $p = .02$] than those on either medication alone. Those subjects on disulfiram were more likely to experience fever [$F(1,242) = 4.63$, $p = .03$] than those on naltrexone, and subjects assigned to naltrexone were more likely to experience nervousness [$F(1,242) = 8.08$, $p = .005$] or restlessness [$F(1,242) = 4.91$, $p = .03$] than those on disulfiram. Those subjects on any medication were more likely to experience aftertaste, blurred vision, confusion, constipation, feeling drowsy, dry mouth, loss of appetite, nausea, or tremors than subjects on placebo. There were no significant group differences in any of the other side effects.

Discussion

The results of this 12-week randomized trial of disulfiram and naltrexone for alcohol use in alcohol-dependent patients with comorbid Axis I disorders suggest that in the context of good alcohol outcomes and good overall compliance, 1) some, but not all, drinking outcomes were significantly better when assigned to any medication versus placebo; 2) there was no clear advantage of the combination of disulfiram and naltrexone over either medication alone; 3) disulfiram had some surprising effects, including a positive effect on craving; and finally 4) these medications, including the combination, had tolerable side effects consistent with those seen in non–dually diagnosed patients. These effects are in a treatment trial in which all treatment groups, including those treated with placebo, experienced substantial and highly significant improvement in drinking outcomes with 177 subjects (69.7%) of all subjects achieving complete abstinence during the 12-week trial.

This study found that the medications to treat alcoholism have a modest advantage to no medication in treating alcohol-dependent patients with comorbid Axis I psychiatric disorders. It must be noted that there was tremendous improvement for patients as a group, even those in the placebo group, suggesting that the treatment as usual or the other nonspecific effects of the research trial were also effective in promoting abstinence. This finding is in a group of patients who were highly motivated because most had already enrolled in a treatment program and all were willing to be randomized to a medication that promotes abstinence (i.e., disulfiram). Because of the high rate of abstinence, the significant medication effects were seen only in the most stringent alcohol outcomes, such as consecutive days of abstinence, and not in the percent of days abstinent or in the percent of heavy drinking days. There were also no group differences in the number of subjects who achieved total abstinence.

Second, the results of this study did not suggest that treatment with the combination of disulfiram and naltrexone was superior to treatment with either medication alone. This occurred in the context that the hypothesized differences between naltrexone and disulfiram were not realized. First, a significant effect of naltrexone on heavy drinking was not seen in this study. As previously highlighted, there was a high rate of abstinence for the subjects as a group overall. If naltrexone's mechanism of action is to reduce the rewarding effect of alcohol (Volpicelli et al 1995; O'Malley 1996), only patients who sample alcohol will find it effective in preventing heavy drinking. It has even been hypothesized that naltrexone treatment is most effective in patients who are actively drinking (Heinala et al 2001; Sinclair 2001). In our study, there was a low rate of overall drinking, and the lack of effect of naltrexone may simply represent a "ceiling" effect. Therefore, in this group of patients, the addition of naltrexone to an antidipsotropic agent may not improve drinking outcomes.

Another finding from this study is that disulfiram had some surprising positive effects. First of all, there was very good overall medication compliance. Contrary to our hypothesis, naltrexone was not superior to disulfiram in terms of overall medication compliance. Although naltrexone may still be more acceptable to patients than disulfiram, particularly in a general clinical setting, in this group of patients who were willing to be randomized to disulfiram, differential rates of medication compliance were not found. This suggests that patients who are willing to initiate disulfiram treatment do not preferentially discontinue its use relative to treatment with naltrexone. Of interest is that naltrexone was also not superior to disulfiram in measures of craving. In fact, in this study, the disulfiram-treated subjects reported lower levels of craving than the naltrexone-treated subjects. Whether this is a direct neurobiological effect of disulfiram on craving or the effect a strong prohibition of drinking has on craving cannot be determined, particularly because disulfiram was not dispensed in a double-blind fashion.

Results from this study suggest that these medications can be used safely but with monitoring, particularly of psychiatric symptoms, in individuals with Axis I comorbid psychiatric disorders and in those who are on psychotropic medications. All subjects included in the study had a major Axis I disorder, a majority was taking psychotropic medications, and many were on more than one psychotropic medication. There were no significant differences in serious adverse effects between these groups. Although there was a significantly higher rate of side effects with the active medications, they were not dissimilar to those reported in previous trials with these agents in non–dually diagnosed individuals (Chick et al 1992; O'Malley et al 1992). Those treated with disulfiram reported more somatic complaints such as nausea and abdominal pain, whereas nervousness and restlessness were associated with treatment with naltrexone. Although subjects as a whole reported an improvement in measures of psychiatric distress, there were also some differences between the groups. Those treated with disulfiram reported fewer anxiety-like symptoms based on the Obsessive–Compulsive and Phobic Anxiety BSI subscales. Those treated with both medications reported higher levels of depression and general distress, based on the somatization and the global severity index. This, and the fact that there were four psychiatric hospitalizations in the disulfiram group, highlights the importance in monitoring psychiatric symptoms in individuals with major Axis I disorders who are prescribed these medications. Of interest is that subjects taking any medication reported lower rates of paranoid ideation, one of most serious psychiatric symptoms, compared with those taking placebo. This directly contradicts early clinical reports, which suggested that disulfiram can actually precipitate psychosis (Larson et al 1992), although those reports were in patients who were prescribed higher doses of disulfiram than those prescribed in this study.

A strength of this study is its large sample size and comprehensive assessment battery to examine changes in behavior associated with medication changes in a "real-world" clinical setting. Several methodologic limitations deserve mention, however. First, this study was based on a predominately male VA sample, and the results may not be generalizable to other clinical

settings. Second, the subjects as a group significantly decreased their alcohol use dramatically, suggesting that nonspecific effects of study participation may have influenced outcome and that there may be some ceiling effects. Third, this study employed a complex study design, in which an open-label medication (disulfiram) was compared with a blinded medication (naltrexone), and there was an imbalance in the number of pills assigned by group. There may have been some differences in patient expectation and in reporting of side effects (e.g., individuals on a known active medication may be more likely to report side effects). Although subjects were randomly assigned to a medication group, whether there were group differences in perception and expectation is not known.

Despite these limitations, this study has both methodologic and clinical importance. It is one of the first studies of which we are aware that evaluates substance use outcomes systematically with the only two FDA-approved medications for alcohol abuse, alone and in combination with dually diagnosed veterans in a "real-world" setting. These results show that these medications can be used safely, albeit with monitoring, in individuals with Axis I psychopathology and in those patients also treated with psychotropic medications. The results suggest naltrexone and disulfiram may be useful pharmacotherapeutic agents for motivated dually diagnosed individuals for maintaining longer periods of abstinence. The combination of these medications offers no advantage, however, and may be a disadvantage in terms of treatment retention. Therefore, the choice of medications can be based on individualized clinical considerations, such as patients' acceptance.

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